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Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

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1. Your reference — P33042-/JDA/BOU

2. Patent application number *(The Patent Office will fill in this part)* — 0301384.4 — 22 JAN 2003

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

   Lux Biotechnology
   4th Floor
   Edinburgh Technology Transfer Centre
   King's Builtings, Mayfield Road
   Edinburgh EH9 3JL

   Patents ADP number *(if you know it)* — 8548299001

   If the applicant is a corporate body, give the country/state of its incorporation

4. Title of the invention — "Device"

5. Name of your agent *(if you have one)* — Murgitroyd & Company

   "Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

   Scotland House
   165-169 Scotland Street
   Glasgow.
   G5 8PL

   Patents ADP number *(if you know it)* — 1198015

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*
   a) any applicant named in part 3 is not an inventor, or
   b) there is an inventor who is not named as an applicant, or
   c) any named applicant is a corporate body.
   See note (d))

   Yes

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	-
Description	9
Claim *(s)*	-
Abstract	-
Drawing *(s)*	2

10. If you are also filing any of the following, state how many against each item.

Priority documents	-
Translations of priority documents	-
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	-
Request for preliminary examination and search *(Patents Form 9/77)*	-
Request for substantive examination *(Patents Form 10/77)*	-
Any other documents *(please specify)*	-

11. I/We request the grant of a patent on the basis of this application.

Signature Murgitroyd & Co   Date 21 January 2003

Murgitroyd & Company

12. Name and daytime telephone number of person to contact in the United Kingdom   Beverley Ouzman   0141 307 8400

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Notes

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Device

The present invention relates to a luminometer calibration device comprising gaseous tritium light source.

Luminometers are devices used to measure the luminous output or luminescence of samples, for example in biotechnology and chemistry. Luminescence is increasingly used as an effective, reliable and safe method for detection and analysis of molecules and living cell dynamics. The luminometer is based on a light-sensitive device termed photomultiplier. It is important that these devices are regularly calibrated to ensure consistency of results. The calibration device may also be used in other luminescence imaging equipment e.g. CCD (Charge Coupled Device) camera based imaging devices such as the "Berthold Night Owl".

Current luminometer calibration devices comprise a plurality of light emitting diodes of varying intensities. The luminometer is calibrated by

checking that the reading of the luminometer corresponds to the known intensity of the light emitted from each of the light emitting diodes.

These known calibration devices are expensive, and require a power source. This renders them relatively untransportable. The known calibration devices are bulky and occupy the entire sample space allocated in the instrument. Thus during calibration of the luminometer, testing must be stopped to place the calibration device into the luminometer. It is not therefore possible to check the calibration of the machine whilst measuring test samples. There is thus a risk that the accuracy of the luminometer may decrease between calibrations, i.e. during testing, so that test results may be inaccurate.

WO 94/05983 discloses a multi-photomultiplier which utilises a radioactive material to provide a light output. Each photomultiplier component of the multi-photomultiplier described in WO 94/05983 is calibrated against another photomultiplier in the same multi-photomultiplier. In contrast the present invention relates to a device of calibrating luminescence imaging or measurement hardware where a gaseous tritium light source provides a light output of predeterminable intensity. The equipment to be tested is compared to a light source of predetermindable intensity rather than being tested relative to another photomultiplier.

According to a first aspect of the present invention there is provided a luminometer calibration device comprising gaseous tritium light source (GTLS) which provides a light output of pre-determinable intensity.

Preferably a number of luminometer calibration devices are provided, each providing a different pre-determinable light intensity. This enables calibration of the luminometer across the whole range of different light intensities. To achieve reduced light intensity, the luminometer calibration device may comprise a light filtering means which predeterminably alters the intensity of the light output to produce a reduced light output. Desirably the calibration devices are selected to test the accuracy of the luminometer across the whole range of light intensity measurable. Preferably the calibration devices can test the accuracy of the luminometer from at least 400 to 650nm, suitably from at least 450 to 610nm.

Tritium ($_3H$) is a radioactive gas that emits electrons which produce light through scintillation when they collide with a phosphor substance. Tritium has a half-life decay of (12.43 +/- 0.05) years and after this time the activity of the tritium source (and thus its luminescence) is decreased by half. The intensity of the light output will slowly decrease over time in accordance with this half-life decay. As the date of manufacture of the luminometer calibration device

is known, the half-life correction may be accurately calculated. The half-life correction may be calculated by means of a computer programme or from a half-life graph.

The luminometer calibration device is desirably small enough to be housed in a sample holder of the luminometer.

Preferably the luminometer calibration device is shaped and sized to be suitable for insertion into an individual well of a standard 96 well plate. As the luminometer calibration device of the present invention is small enough to be housed in a single well of a sample holder of the luminometer, it is possible for the calibration device to be left in the luminometer during use, even when other wells contain test materials. The GTLS is typically 4.5mm x 1.6mm other sized samples may be used however.

The calibration of the luminometer can therefore be checked for accuracy at each instance of use of the calibration device of the present invention.

Preferably the GTLS is sealed in a housing which is not easily broken under normal working conditions. Suitably the housing is shatter, heat, cold and moisture resistant. Suitable materials for the housing include any material which is transparent or translucent (i.e. permits transmission of luminescence) and is unreactive to tritium.

Mention may be made of glass, plastic and a combination of these materials.

Optionally, the housing for the GTLS is itself placed into a chamber housing having at least one optically transparent or translucent end to permit transmission of the luminescence from the tritium source. The chamber facilitates easy handling of the housing which is generally small and also acts as a suitable receptacle for holding any light filter required. The chamber is typically formed from metal, preferably stainless steel. The translucent end is suitably formed from glass or plastic.

The luminometer calibration device may comprise colouring means to alter the colour of the light output to produce a coloured light output.

Typically the GTLS comprises 10 to 20 mCi of tritium, suitably 15 to 20 mCi, preferably 18 mCi (0.666 GBG) of tritium.

According to a further aspect of the present invention there is provided a kit comprising two or more luminometer calibration devices as described above each providing a light output of pre-determinable and distinct intensity. Thus each of the luminometer calibration devices provides a light output of a different pre-determinable intensity to the other devices present in the kit, and suitably the different intensities provided

span the entire range of light intensity measurable by the luminometer.

The kit may also include indicia recording the date(s) of manufacture of the devices, and means to calculate the intensity of the light output at any time from the date(s) of manufacture.

The kit may also comprise colouring means to alter the colour of the light output. Suitably the light output of each luminometer calibration device is altered by the colouring means, to a different colour, and the kit provides a range of colour light outputs.

Preferably the colouring means comprises one or more phosphors. Suitably the colouring means is provided by a phosphor coating on the GTLS housing.

According to a further aspect of the present invention there is provided a colourimetric equipment calibration device having a luminescent sample comprising GTLS which provides a light output of pre-determinable intensity and colouring means to alter the colour of the light output to produce a coloured light output.

According to a further aspect of the present invention there is provided a method of calibrating a luminometer comprising the steps of;

placing a calibration device comprising gaseous tritium light source (GTLS) which provides a light output of pre-determinable intensity in the luminometer; and

adjusting the reading of light output of the luminometer to the pre-determined intensity of the light output of the calibration device.

Where the calibration device comprises colouring means to alter the colour of the light output to produce a coloured light output, the luminometer tested may be colourimetric equipment.

According to a further aspect of the present invention there is provided a luminometer comprising a luminometer calibration device comprising GTLS, wherein the luminometer calibration device is housed in a sample holder of the luminometer.

According to a further aspect of the present invention there is provided a method of detecting and/or analysing the dynamics of molecules and/or living cells comprising the steps of putting a sample comprising molecules and/or living cells in a luminometer and noting the light absorption of the sample wherein a luminometer calibration device comprising tritium which provides a light output of pre-determinable intensity is used as a standard.

The present invention will now be described by way of example only with reference to the accompanying drawings in which;

Fig. 1 shows a perspective elevational view of a kit of luminometer calibration devices; and

Fig. 2 shows a diagrammatic view of a readout from a luminometer/plate reader.

Fig. 1 shows a kit 10 comprising nine luminometer calibration devices 12. Each luminometer calibration device comprises a tritium sample 14 which provides a light output of pre-determinable intensity. The tritium 14 is sealed in a generally tubular housing 16 formed from clear glass, internally coated with phosphor. The tritium sample 14 and housing 16 are located within a cylindrical chamber 18. The side 20 of the cylindrical chamber 18 is formed from metal, such as stainless steel. The cylindrical chamber 18 has top and bottom end portions, 22, 24. The bottom end portion 24 is formed from transparent material, such as glass or plastic. A light filtering means 26 is located between the tritium sample 14, and the bottom end portion 24. The light filtering means 26 predeterminably alters the intensity of the light output to produce a reduced light output. The filter consists of Kodak "Wratten" neutral density filter which transmits specific percentage of light e.g. 90%, 10% 1% 0.2% The effect of the light filtering means 26 in each luminometer

calibration device 12 is different, and thus the intensity of the light output of each luminometer calibration device 12 is also different, thus providing a range of light output intensities. The light output range from 400 to 700nm, and there is a light output at 450 +/- 10nm, 525 +/- 5nm and 610 +/- 10nm. The housing 16 of the tritium sample 14 is internally coated with a phosphor which changes the colour of the light output to produce a coloured light output. The housing 16 of each luminometer calibration device 12 is coated with a different phosphor and the light output of each luminometer calibration device is a different colour.

Fig. 2 shows a luminometer/plate reader showing the light output of the kit of luminometer calibration devices 12 as shown in Fig. 1. All of the luminometer calibration devices 12 have a light output of different intensities, and of different colours.

Fig. 1

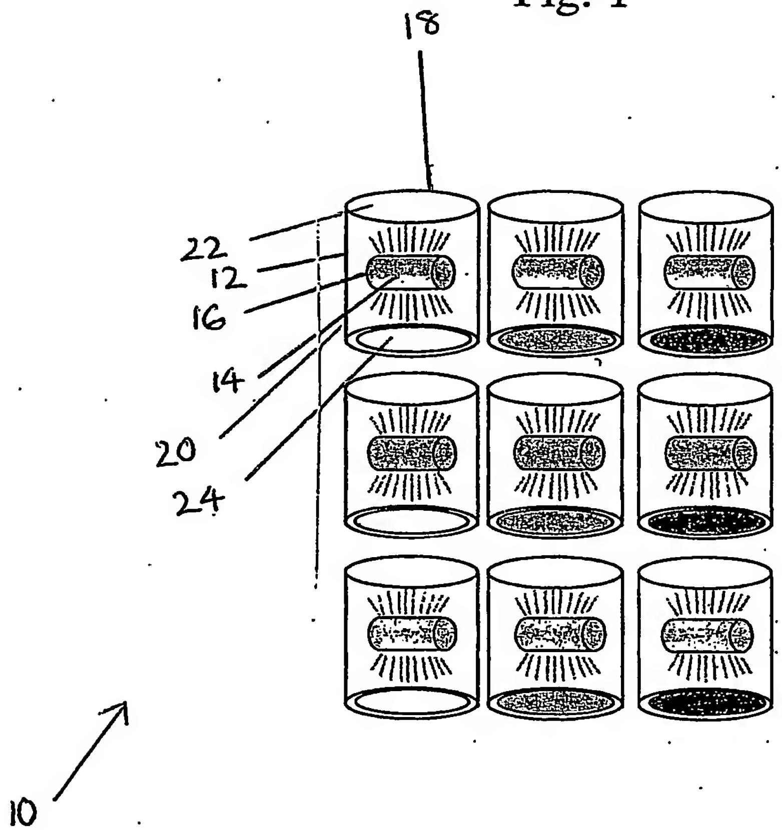
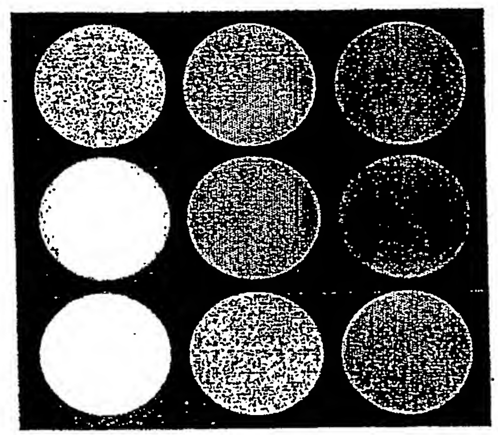


Fig. 2



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